Ribavirin

Brand Name: Virazole, Rebetol, Copegus

Drug Description

Ribavirin is a synthetic nucleoside agent that has a broad spectrum of antiviral activity against both DNA and RNA viruses. [1] Ribavirin is structurally related to pyrazofurin (pyrazomycin), guanosine, and xanthosine. [2]

HIV/AIDS-Related Uses

HIV infected patients are commonly coinfected with hepatitis C virus (HCV). Interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b in conjunction with oral ribavirin are regimens often prescribed for the treatment of chronic HCV infection with compensated liver disease in patients who have not previously received interferon therapy. Although therapy with oral ribavirin alone is not effective for the treatment of chronic HCV infection, use of the drug in conjunction with an interferon alfa preparation has been shown to increase the rate of sustained response by two- to three-fold and decrease the rate of relapse following discontinuance of therapy. The highest rates of sustained virologic response and the lowest rates of relapse have been achieved with concomitant use of peginterferon alfa and oral ribavirin. Interferon monotherapy generally is reserved for use in patients in whom ribavirin is contraindicated or not tolerated.[3]

Oral ribavirin monotherapy has been investigated for use in the management of HIV infection; however, the results of several limited studies in patients with HIV infection have failed to show evidence of beneficial effects.[4]

Ribavirin is being studied in combination with peginterferon alfa-2a and adefovir dipivoxil in patients triple-infected with HIV, HCV, and hepatitis B virus (HBV).[5]

Non-HIV/AIDS-Related Uses

Ribavirin is indicated in combination with interferon alfa-2a or -2b or peginterferon alfa-2a or -2b for the treatment of chronic HCV infection in patients who have compensated liver disease and have not been previously treated with interferon alfa and are at least 18 years of age who have relapsed after interferon alfa therapy.[6]

Ribavirin inhalation solution is indicated as a primary agent in the treatment of lower respiratory tract disease (including bronchiolitis and pneumonia) caused by respiratory syncytial virus (RSV) in hospitalized infants and young children who are at high risk for severe or complicated RSV infection. This category includes premature infants and infants with structural or physiologic cardiopulmonary disorders, bronchopulmonary dysplasia, immunodeficiency or imminent respiratory failure. Ribavirin is also indicated in the treatment of RSV infections in infants requiring mechanical ventilator assistance.[7] Ribavirin is used via nasal or oral inhalation in the treatment of these severe lower respiratory tract infections.[8]

Orally ingested ribavirin has been used with some success for the treatment of various strains of influenza A virus and influenza B virus. Inhalation therapy with ribavirin is currently being studied for the treatment of these viruses.[9]

Ribavirin has been used for the treatment of a variety of viral hemorrhagic fevers, including Lassa fever, Hantavirus infections, and Crimean-Congo hemorrhagic fever. Viral hemorrhagic fevers are a diverse group of infections caused by RNA viruses from several viral families. Ribavirin is the only antiviral agent identified to date that exhibits potential efficacy for the management of some viral hemorrhagic fevers.[10]

Pharmacology

The mechanism of action of ribavirin's antiviral activity has not been fully elucidated, but the drug appears to interfere with RNA and DNA synthesis and subsequently inhibit protein synthesis and viral replication. The drug's antiviral activity results principally in an intracellular virustatic effect in cells infected with ribavirin-sensitive RNA or DNA viruses; however, its specific mechanisms of action may vary depending on the virus. The antiviral activity of ribavirin appears to depend principally on intracellular conversion of the drug to ribavirin-5'-triphosphate (RTP) and

Ribavirin

Pharmacology (cont.)

-monophosphate. Ribavirin is phosphorylated to ribavirin-5'-monophosphate, -diphosphate, and -triphosphate. Phosphorylation of ribavirin occurs principally in virus-infected cells but also occurs in uninfected cells. Formulation of ribavirin-5'-monophosphate appears to be the rate-limiting step in the formation of ribavirin-5'-triphosphate. RTP competes with adenosine-5'-triphosphate and guanosine-5'-triphosphate for viral RNA polymerase.[11] RTP is a potent competitive inhibitor of inosine monophosphate dehydrogenase, influenza virus RNA polymerase, and messenger RNA (mRNA) guanylyltransferase, the latter resulting in inhibition of the capping of mRNA. These diverse effects markedly reduce intracellular guanosine triphosphate pools and inhibit viral RNA and protein synthesis.[12]

When administered orally, ribavirin is rapidly absorbed from the gastrointestinal (GI) tract, with bioavailibility approximately 45%.[13] A small amount of ribavirin is absorbed systemically from the respiratory tract following nasal and oral inhalation. The bioavailability of inhaled ribavirin may depend on the method of drug delivery during nebulization. At a contact flow rate, the amount of drug delivered to the respiratory tract theoretically is directly related to the concentration of nebulized drug solution and the duration of inhalation therapy. Peak plasma ribavirin concentrations generally occur at the end of the inhalation period, when the drug is inhaled orally and nasally using a small-particle aerosol generator, and increase with longer duration of the inhalation period.[14] Ribavirin is readily absorbed across the cellular plasma membrane, probably via a nucleoside transport mechanism. Ribavirin has two pathways of metabolism: 1) a reversible phosphorylation pathway in nucleated cells; and 2) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite.[15]

Ribavirin distributes to plasma, respiratory tract secretions, and erythrocytes (RBCs); following nasal and oral inhalation, the highest ribavirin concentrations are found in the respiratory tract and RBCs.[16] Large amounts of ribavirin triphosphate are sequestered in RBCs, reaching a plateau in approximately 4 days and remaining sequestered for weeks after administration. Time to peak plasma concentration (Cmax) for IV doses is reached at the end of infusion; for oral doses, it is 1 to 1.5 hours. Therapeutically effective concentrations depend primarily on the duration of exposure and patient minute volume. Concentrations in respiratory tract secretions are much higher than corresponding plasma concentrations.[17] Following oral administration of a single 3 mg/kg dose, RBC concentrations of ribavirin have been reported to peak within approximately 4 days, exceeding concurrent plasma concentrations at 4 days by about 100-fold, then declining with a half-life of about 40 days (the half-life of RBCs). During the initial 1 to 2 hours following oral administration, RBC concentrations increase at a rate similar to plasma concentrations; thereafter, RBC concentrations continue to increase for about 4 days as plasma drug concentrations decline. Significant concentrations (greater than 67%) may be found in the cerebrospinal fluid (CSF) after prolonged administration. Ribavirin appears to distribute slowly into CSF. Following chronic (4 to 7 weeks) oral administration of ribavirin in patients with AIDS or AIDS-related complex, CSF concentrations of the drug were approximately 70% of concurrent plasma concentrations.[18]

Ribavirin is in FDA Pregnancy Category X. No studies have been done in pregnant women; however, ribavirin is contraindicated during pregnancy. Studies in primates (e.g., baboons) have not shown that ribavirin causes adverse effects on the fetus; however, results from studies in other animals have shown that it is teratogenic and/or embryocidal in nearly all species tested, with effects including reduced survival of fetuses and offspring and malformation of the skull, palate, eye, jaw, skeleton, and GI tract. Health care workers and visitors who spend time at the patient's bedside may become environmentally exposed to ribavirin. Female health care workers and visitors who are pregnant, or may become pregnant, should be advised of the potential risks of exposure. It is not known if ribavirin is excreted into human breast milk. It does distribute into the breast milk of other species and has been shown to harm lactating animals and their offspring.[19]

Ribavirin

Pharmacology (cont.)

Plasma protein binding of ribavirin is insignificant. The elimination half-life of an IV or oral dose is approximately 0.5 to 2 hours; for inhaled ribavirin, the elimination half-life is 9.5 hours. The terminal half-life of a single dose of IV or oral ribavirin is 27 to 36 hours, reaching steady state at approximately 151 hours. Ribavirin is excreted principally in urine. For ribavirin administered for inhalation, renal elimination is approximately 30% to 55% excreted as the 1,2,4-triazole carboxamide metabolite in urine within 72 to 80 hours. In healthy adults with normal renal function, approximately 53% of a single oral dose is excreted in urine within 72 to 80 hours, with about 33% excreted in the first 24 hours. Approximately 37%, 30%, and 30% of the fraction excreted in urine appears as unchanged drug, 1,2,4-triazole-3-carboxamide, and 1,2,4-triazole-3-carboxylic acid, respectively, within 1.5 to 2 hours, and approximately 17%, 50%, and 22%, respectively, within 24 hours.[20] Significant amounts of ribavirin are not removed by hemodialysis. Approximately 15% of an inhaled dose of ribavirin is excreted in feces within 72 hours. Approximately 19% of IV ribavirin is excreted unchanged in 24 hours; approximately 24% is excreted unchanged in 48 hours. Approximately 7% of an oral dose of ribavirin is excreted unchanged in 24 hours; approximately 10% is excreted unchanged in 48 hours.[21] Plasma concentrations of ribavirin appear to decline in a manner dependent on the route of administration.[22]

Development of resistance to the antiviral activity of ribavirin has not been fully evaluated. Unlike the viral response to some other currently available antiviral agents (e.g., acyclovir, amantadine), most susceptible viruses do not appear to develop resistance to ribavirin despite repeated exposure. This may be due to ribavirin's multiple mechanisms of action.[23]

Adverse Events/Toxicity

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 13% of patients treated with ribavirin and peginterferon alfa-2a[24] and 10% of patients treated with ribavirin and interferon alfa-2b.[25] [26] The anemia associated with ribavirin occurs within the first 1 to 2 weeks of oral therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained pretreatment and at weeks 2 and 4 of therapy or more frequently if clinically indicated. Patients should then be followed as clinically appropriate.[27] [28]

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment and should be monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin.[29] [30]

Sudden deterioration of respiratory function has been associated with aerosolized ribavirin use in infants; respiratory function should be carefully monitored during treatment. If initiated aerosolized ribavirin treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and reinstated only with extreme caution, continuous monitoring and consideration of concomitant administration of bronchodilators.[31]

Some common adverse effects observed with IV and oral ribavirin are central nervous system effects (fatigue, headache, insomnia) and GI effects (anorexia, nausea). Skin irritation due to prolonged drug contact and skin rash is observed in patients who receive ribavirin via inhalation, and health care workers who help in the administration of inhaled doses sometime exhibit headache and itching, redness, or swelling of the eyes.[32]

Drug and Food Interactions

The manufacturer of ribavirin states that concomitant use of ribavirin and nucleoside analogues should be undertaken with caution and

Drug and Food Interactions (cont.)

only if the potential benefits outweigh the potential risks. Use of ribavirin and nucleoside reverse transcriptase inhibitors may increase the risk of mitochondrial dysfunction and other associated toxicities.[33] In addition, in vitro studies have shown that when combined, ribavirin and zidovudine are reproducibly antagonistic and should not be used concurrently.[34] Ribavirin inhibits the phosphorylation of zidovudine and stavudine to its active triphosphate form, which could lead to decreased antiretroviral activity. Exposure to didanosine or its active metabolite (didoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin, which could cause or worsen clinical toxicities.[35] Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactactemia/lactic acidosis have been reported in clinical trials.[36]

Both area under the plasma concentration-time curve (AUC) and Cmax increased by 70% when ribavirin capsules were administered with a high-fat meal in a single-dose pharmacokinetic study. There are insufficient data to address the clinical relevance of these results. Ribavirin capsules taken with an antacid containing magnesium, aluminum, and simethicone resulted in a 14% decrease in mean ribavirin AUC.[37] [38]

The manufacturer of ribavirin for nasal and oral inhalation states that the potential for drug interactions have not been evaluated in patients receiving ribavirin concomitantly with digoxin, diuretics, respiratory smooth muscle relaxants (e.g., theophylline), anti-infective agents, antimetabolites, or other antiviral agents. However, some data indicate that the in vitro and in vivo antiviral activity of ribavirin against some viruses (e.g., influenza virus) may be enhanced by other antiviral agents (e.g., amantadine, rimantadine).[39]

Contraindications

Because ribavirin may cause birth defects and/or death of the exposed fetus, it is contraindicated for use in women who are pregnant or in men whose female partners are pregnant. Ribavirin is also contraindicated in patients with a hypersensitivity to the drug or any of its components and in patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia).[40] [41] Patients who have autoimmune hepatitis or hepatic decompensation (Child-Pugh class B and C) must not be treated with ribavirin combination therapy that includes interferon alpha.[42]

IV and oral ribavirin may cause anemia that is reversible when the drug is discontinued.[43]

Clinical Trials

For information on clinical trials that involve Ribavirin, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Ribavirin AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[44] [45] [46] Mode of Delivery:

Inhalation.[47]

Dosage Form: Capsules and tablets containing 200 mg of ribavirin.[48] [49]

Glass vials containing 6 g of lyophilized ribavirin powder per 100 ml for reconstitution into solution for inhalation.[50]

Storage: Store capsules or tablets at 25 C (77 F); excursions are permitted between 15 C to 30 C (59 F to 86 F).[51] [52] Keep bottle tightly closed.[53] Store ribavirin oral solution between 2 C and 8 C (36 F and 46 F) or at 25 C (77 F); excursions are permitted to 15 C to 30 C (59 F to 86 F).[54]

Vials containing lyophilized ribavirin for reconstitution for inhalation should be stored in a dry place at 15 C to 25 C (59 F to 78 F).[55]

Chemistry

CAS Name: 1-beta-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide[56]

CAS Number: 36791-04-5[57]

Molecular formula: C8-H12-N4-O5[58]

Ribavirin

Chemistry (cont.)

C39.35%, H4.95%, N22.94%, O32.76%[59]

Molecular weight: 244.20[60]

Melting point: 166 C to 168 C (aqueous ethanol); 174 C to 176 C (ethanol)[61]

Physical Description: Ribavirin is a white, crystalline powder.[62]

Stability: Reconstituted solutions of ribavirin for inhalation may be stored for up to 24 hours at room temperature, 20 C to 30 C (68 F to 86 F).[63]

Solubility: Ribavirin has a maximum solubility in water of 142 mg/ml at 25 C and only a slight solubility in ethanol.[64] Ribavirin is slightly soluble in anhydrous alcohol.[65]

Other Names

Ribamide[66]

Viramide[67]

Ribamidil[68]

Ribamidyl[69]

Ribavirina[70]

Ribovirin[71]

Tribavirin[72]

Further Reading

Brennan C. Treatment of hepatitis C virus in the coinfected patient. J Assoc Nurses AIDS Care. 2003 Sep-Oct;14(5 Suppl):52S-79S. Review. PMID: 14571561

Medina J, Garcia-Buey L, Moreno-Monteagudo JA, Trapero-Marugan M, Moreno-Otero R. Combined antiviral options for the treatment of chronic hepatitis C. Antiviral Res. 2003 Oct;60(2):135-43. Review. PMID: 14638410

Perez-Olmeda M, Soriano V, Asensi V, Morales D, Romero M, Ochoa A, Sanchez-Montero F, Santin M, Guardiola J, Blanch J, Nunez M, Jimenez-Nacher I, Garcia-Samaniego J; The HCV/HIV Spanish Study Group. Treatment of chronic hepatitis C in HIV-infected patients with interferon alpha-2b plus ribavirin. AIDS Res Hum Retroviruses. 2003 Dec;19(12):1083-9. PMID: 14709244

Rockstroh JK. Management of hepatitis B and C in HIV co-infected patients. J Acquir Immune Defic Syndr. 2003 Sep;34 Suppl 1:S59-65. Review. PMID: 14562859

Romero M, Perez-Olmeda M, Garcia-Samaniego J, Soriano V. Management of chronic hepatitis C in patients co-infected with HIV: focus on safety considerations. Drug Saf. 2004;27(1):7-24. PMID: 14720084

Manufacturer Information

Ribavirin
Valeant Pharmaceuticals International
Valeant Plaza
3300 Hyland Avenue
Costa Mesa, CA 92626
(800) 548-5100

Virazole
Valeant Pharmaceuticals International
Valeant Plaza
3300 Hyland Avenue
Costa Mesa, CA 92626
(800) 548-5100

Rebetol
Schering - Plough Corp
2000 Galloping Hill Rd
Kenilworth, NJ 07033-0530
(800) 526-4099

Copegus
Roche Laboratories
340 Kingsland Street
Nutley, NJ 07110
(973) 235-5000

Ribavirin

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. AHFS Drug Information - 2003; p. 578

2. AHFS Drug Information - 2003; p. 589

3. AHFS Drug Information - 2003; p. 579-580

4. AHFS Drug Information - 2003; p. 581

5. Protocol ID: ACTG A5149 - p. 12

6. Schering Plough - Rebetol Prescribing Information, September 2002, p.1. Available at http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

7. USP DI - 2004; p. 2447

8. AHFS Drug Information - 2003; p. 578

9. AHFS Drug Information - 2003; p. 580

10. AHFS Drug Information - 2003; p. 580

11. AHFS Drug Information - 2003; p. 587

12. USP DI - 2004; p. 2447

13. USP DI - 2004; p. 2447

14. AHFS Drug Information - 2003; p. 589

15. Schering Plough - Rebetol Prescribing Information, September 2002, p.1. Available at http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

16. AHFS Drug Information - 2003; p. 587

17. USP DI - 2004; p. 2447

18. AHFS Drug Information - 2003; p. 587

19. USP DI - 2004; p. 2448

20. AHFS Drug Information - 2003; p. 587

21. USP DI - 2004; p. 2447

22. AHFS Drug Information - 2003; p. 587

23. AHFS Drug Information - 2003; p. 588-589

24. Roche Laboratories - Copegus Prescribing Information, May 2004, p. 8. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 06/21/04.

25. Schering Plough - Rebetol Prescribing Information, March 2003, p. 2. Available at http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

26. AHFS Drug Information - 2003; p. 583

27. Roche Laboratories - Copegus Prescribing Information, May 2004, p. 8. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 06/21/04.

28. Schering Plough - Rebetol Prescribing Information, March 2003, p. 2. Available at http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

29. Schering Plough - Rebetol Prescribing Information, March 2003, p. 2. Available at http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

30. Roche Laboratories - Copegus Prescribing Information, May 2004, p. 8. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 06/21/04.

31. Valeant Pharmaceuticals International - Virazole Prescribing Information, p. 1. Available at http://www.virazole.com/prescribing.html. Accessed 06/21/04.

32. USP DI - 2004; p. 2448

33. AHFS Drug Information - 2003; p. 587

34. USP DI - 2004; p. 2448

35. Roche Laboratories - Copegus Prescribing Information, May 2004, p. 4. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 06/21/04.

36. Schering Plough - Rebetol Prescribing Information, March 2003, p. 3. Available at http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

37. AHFS Drug Information - 2003; p. 587

38. Schering Plough - Rebetol Prescribing Information, March 2003, p. 1. Available at http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

39. AHFS Drug Information - 2003; p. 587

40. Schering Plough - Rebetol Prescribing Information, March 2003, p. 2. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

41. Roche Laboratories - Copegus Prescribing Information, May 2004, p. 6. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 06/21/04.

42. Roche Laboratories - Copegus Prescribing Information, May 2004, p. 6. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 06/21/04.

43. USP DI - 2004; p. 2448

44. USP DI - 2004; p. 2449-2450

45. Schering Plough - Rebetol Prescribing Information, September 2002, p. 4. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

46. Roche Laboratories - Copegus Prescribing Information, May 2004, pp. 17-18. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 06/21/04.

47. Valeant Pharmaceuticals International - Virazole Prescribing Information, p. 1. Available at http://www.virazole.com/prescribing.html. Accessed 06/21/04.

48. Roche Laboratories - Copegus Prescribing Information, May 2004, p. 17. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 06/21/04.

49. Schering Plough - Rebetol Prescribing Information, September 2002, p. 4. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

50. Valeant Pharmaceuticals International - Virazole Prescribing Information, p. 8. Available at http://www.virazole.com/prescribing.html. Accessed 06/21/04.

51. Schering Plough - Rebetol Prescribing Information, September 2002, p. 4. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

52. Roche Laboratories - Copegus Prescribing Information, May 2004, p. 18. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 06/21/04.

53. Roche Laboratories - Copegus Prescribing Information, May 2004, p. 18. Available at: http://www.rocheusa.com/products/copegus/pi.pdf. Accessed 06/21/04.

54. Schering Plough - Rebetol Prescribing Information, September 2002, p. 4. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

55. Valeant Pharmaceuticals International - Virazole Prescribing Information, p. 8. Available at http://www.virazole.com/prescribing.html. Accessed 06/21/04.

56. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/. Accessed 06/21/04.

57. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/. Accessed 06/21/04.

58. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/. Accessed 06/21/04.

59. Merck Index - 2001; p. 1469

60. Merck Index - 2001; p. 1469

61. Merck Index - 2001; p. 1469-1470

62. Schering Plough - Rebetol Prescribing Information, September 2002, p. 1. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

63. Valeant Pharmaceuticals International - Virazole Prescribing Information, p. 8. Available at http://www.virazole.com/prescribing.html. Accessed 06/21/04.

64. Valeant Pharmaceuticals International - Virazole Prescribing Information, p. 2. Available at http://www.virazole.com/prescribing.html. Accessed 06/21/04.

65. Schering Plough - Rebetol Prescribing Information, September 2002, p. 1. Available at: http://www.spfiles.com/pirebetol.pdf. Accessed 06/21/04.

66. ChemIDplus. - Available at: http://chem.sis.nlm.nih.gov/chemidplus/. Accessed 06/21/04.

67. MeSH - Available at: http://www.nlm.nih.gov/mesh/Mbrowser.html. Accessed 06/21/04.

68. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/. Accessed 06/21/04.

69. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/. Accessed 06/21/04.

70. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/. Accessed 06/21/04.

71. MeSH - Available at: http://www.nlm.nih.gov/mesh/Mbrowser.html. Accessed 06/21/04.

72. ChemIDplus - Available at: http://chem.sis.nlm.nih.gov/chemidplus/. Accessed 06/21/04.